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FORM PTO-1390 (REV 11-2000)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER <b>512100-2022</b>
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>			U.S. APPLICATION NO. (If known see 37 C.F.R. 1.5) <b>09/936503</b>
INTERNATIONAL APPLICATION NO. <b>PCT/EP00/02042</b>	INTERNATIONAL FILING DATE <b>09 MARCH 2000</b>	PRIORITY DATE CLAIMED <b>18 MARCH 1999</b>	
TITLE OF INVENTION <b>TRANSDERMAL THERAPEUTIC SYSTEM AND PROCESS FOR ITS PRODUCTION</b>			
APPLICANT(S) FOR DO/EO/US <b>Robert-Peter KLEIN, Reinhold MECONI</b>			
<p>Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:</p> <ol style="list-style-type: none"> <li><input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li><input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li><input checked="" type="checkbox"/> This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).</li> <li><input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).</li> <li><input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))             <ol style="list-style-type: none"> <li><input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</li> <li><input type="checkbox"/> has been communicated by the International Bureau.</li> <li><input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> </li> <li><input checked="" type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).</li> <li><input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))             <ol style="list-style-type: none"> <li><input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</li> <li><input type="checkbox"/> have been communicated by the International Bureau.</li> <li><input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li><input checked="" type="checkbox"/> have not been made and will not be made.</li> </ol> </li> <li><input type="checkbox"/> A English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li><input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</li> <li><input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</li> </ol> <p><b>Items 11 to 20 below concern document(s) or information included:</b></p> <ol style="list-style-type: none"> <li><input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li><input checked="" type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li><input checked="" type="checkbox"/> A FIRST preliminary amendment.</li> <li><input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</li> <li><input type="checkbox"/> A substitute specification.</li> <li><input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li><input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.</li> <li><input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</li> <li><input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</li> <li><input checked="" type="checkbox"/> Other items or information: PCT/RO/101, PCT/ISA/210, PCT/IPEA/416, 409, PCT/IB/308, 2 sheets of drawings</li> </ol>			

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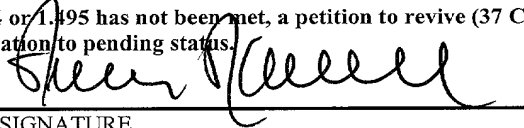
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U.S. APPLICATION NO. <b>09/936503</b> INTERNATIONAL APPLICATION NO. PCT/EP00/02042		ATTORNEY'S DOCKET NO. 512100-2022																																														
21. <input checked="" type="checkbox"/> The following fees are submitted		CALCULATIONS PTO USE ONLY																																														
<b>BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO..... \$1000.00  International preliminary examination fee (37 C.F.R. 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO..... \$860.00  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO... \$710.00  International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$690.00  International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ... \$100.00		<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td colspan="2"><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b></td> <td style="text-align: right;"><b>\$ 860.00</b></td> </tr> <tr> <td colspan="2">           Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30            months from the earliest claimed priority date (37 CFR 1.492(e)).         </td> <td style="text-align: right;">\$</td> </tr> <tr> <td style="text-align: center;">CLAIMS</td> <td style="text-align: center;">NUMBER FILED</td> <td style="text-align: center;">NUMBER EXTRA</td> </tr> <tr> <td>Total Claims</td> <td style="text-align: center;"><b>6 - 20 =</b></td> <td style="text-align: center;"><b>0</b></td> </tr> <tr> <td>Independent Claims</td> <td style="text-align: center;"><b>3 - 3 =</b></td> <td style="text-align: center;"><b>0</b></td> </tr> <tr> <td colspan="2">MULTIPLE DEPENDENT CLAIM(S) (if applicable)</td> <td style="text-align: center;"><b>+ \$270.00</b></td> </tr> <tr> <td colspan="2"><b>TOTAL OF ABOVE CALCULATIONS =</b></td> <td style="text-align: right;"><b>\$</b></td> </tr> <tr> <td colspan="2"> <input type="checkbox"/> Applicant claims small entity status. See 37 C.F.R. 1.27. The fees indicated            above are reduced by 1/2.         </td> <td style="text-align: right;">\$</td> </tr> <tr> <td colspan="2"><b>SUBTOTAL =</b></td> <td style="text-align: right;"><b>\$</b></td> </tr> <tr> <td colspan="2">           Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30            months from the earliest claimed priority date (37 CFR 1.492(f)).         </td> <td style="text-align: right;">\$</td> </tr> <tr> <td colspan="2"><b>TOTAL NATIONAL FEE =</b></td> <td style="text-align: right;"><b>\$ 860.00</b></td> </tr> <tr> <td colspan="2">           Fee for recording the enclosed assignments (37 CFR 1.21(h)). The assignment must be            accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property         </td> <td style="text-align: right;">\$</td> </tr> <tr> <td colspan="2"><b>TOTAL FEES ENCLOSED =</b></td> <td style="text-align: right;"><b>\$ 900.00</b></td> </tr> <tr> <td colspan="2"></td> <td style="text-align: right;">Amount to be refunded: \$</td> </tr> <tr> <td colspan="2"></td> <td style="text-align: right;">Charged: \$</td> </tr> </table>		<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>		<b>\$ 860.00</b>	Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		\$	CLAIMS	NUMBER FILED	NUMBER EXTRA	Total Claims	<b>6 - 20 =</b>	<b>0</b>	Independent Claims	<b>3 - 3 =</b>	<b>0</b>	MULTIPLE DEPENDENT CLAIM(S) (if applicable)		<b>+ \$270.00</b>	<b>TOTAL OF ABOVE CALCULATIONS =</b>		<b>\$</b>	<input type="checkbox"/> Applicant claims small entity status. See 37 C.F.R. 1.27. The fees indicated above are reduced by 1/2.		\$	<b>SUBTOTAL =</b>		<b>\$</b>	Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).		\$	<b>TOTAL NATIONAL FEE =</b>		<b>\$ 860.00</b>	Fee for recording the enclosed assignments (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property		\$	<b>TOTAL FEES ENCLOSED =</b>		<b>\$ 900.00</b>			Amount to be refunded: \$			Charged: \$
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NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.																																																
SEND ALL CORRESPONDENCE TO:  <b>WILLIAM F. LAWRENCE, ESQ.</b> <b>FROMMER LAWRENCE &amp; HAUG LLP</b> <b>745 FIFTH AVENUE</b> <b>NEW YORK, NEW YORK 10151</b>  Dated: <u>September 13, 2001</u>																																																
<div style="text-align: center;">             SIGNATURE             William F. Lawrence            NAME             28,029            REGISTRATION NUMBER         </div>																																																

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: KLEIN, et al.

Filed.: Filed Concurrently Herewith

Title of Invention: TRANSDERMAL THERAPEUTIC SYSTEM AND  
PROCESS FOR ITS PRODUCTION

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New York, NY 10151

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**PRELIMINARY AMENDMENT**

Assistant Commissioner for Patents  
Box PCT  
Washington, D.C. 20231

Sir:

Before the issuance of the first Office Action, please amend the above-identified application as follows:

**IN THE CLAIMS:**

Please amend Claim 5 as follows:

5. (Amended) The embodiment as claimed in claim 1, wherein the paper has a basis weight of from 9 to 60, preferably from 15 to 40 and particularly from 20 to 35 g/m<sup>2</sup>.

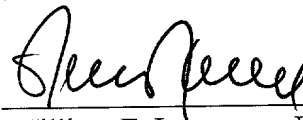
**REMARKS**

Claim 5 has been amended to correct a multiple claim dependency. The filing fee has been calculated based the amendment to the claim. The attached is captioned "**Version with markings to show changes made**" and indicate the changes that have been made herein.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP  
Attorneys for Applicant

By:



William F. Lawrence, Esq.  
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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**Claim 5 has been amended as follows:**

5. The embodiment as claimed in [one or more of claims 1-4] claim 1, wherein the paper has a basis weight of from 9 to 60, preferably from 15 to 40 and particularly from 20 to 35 g/m<sup>2</sup>.

2/parts

**Transdermal Therapeutic System and Process for its Production**

## Specification

- 5 The invention relates to a transdermal therapeutic system (TTS) and a process for its production.

10 Therapeutic systems for the transdermal administration of pharmaceuticals, such as nicotine, nitroglycerine, sexual hormones, scopolamine, fentanyl are known. Suitable systems have for example been described in international application DE 87/00372 (WO 88/01516). Such systems contain as essential features a backing layer which is remote from the skin and impermeable for the active substance, at least one active substance depot, an active substance distribution device which is in contact with the active substance depot, a control device which controls the delivery of the active substance by the system, and a pressure-sensitive adhesive fixing device for the therapeutic system on the skin. The active substance distribution device may be combined with the control device to yield a reservoir matrix which has one or more discrete active substance depots arranged in spatially defined manner with respect to one another and having a higher active substance concentration than that which is present in the reservoir matrix.

It is stated in WO 88/01516 that the depot may also contain inert adjuvants such as support materials which make the active substance depot insensitive with respect to application of pressure and tension, and carriers. According to US patent specification 5,820,876 the support material may be a planar fabric (support fabric) as an inert adjuvant, by which the distribution of the active substance within the depot is effected and favored. A particular embodiment is also disclosed in Figure 5 of both documents, according to which an adhesive layer is provided on a backing layer, upon which the active substance is present, if desired with adjuvants, such as material for facilitating the processability of the active substance, or carrier materials such as fabrics. The support fabric may also be present as a non-woven fabric (fleece). In the examples fleece materials are disclosed as being suitable (50:50 viscose rayon-cotton fiber blend with a substance weight of 80 g/m<sup>2</sup>, Paratex II/80 of the company Lohmann GmbH & Co. KG, or a 70:30 viscose rayon-cotton fiber blend with a substance weight of 40 g/m<sup>2</sup>, Paratex III/40 of the company Lohmann GmbH & Co. KG). In both examples it is additionally stated that the fleece material acts as a support fabric and also to assist the uniform distribution of the nicotine, as an inert adjuvant as defined in the introductory part of the specification.

US patent specification 4,597,961 discloses a different form of a transdermal therapeutic system. In this system the delivery of the active substance is generally controlled by a microporous membrane. It is stated in the description of Figure 2 that reservoir 114 can contain a suitable absorbent material 122, such as a sponge or cotton, on which is absorbed the desired quantity of liquid nicotine. Additionally it is pointed out in Example 4 that reservoir 114 contains a dense matrix of inert fibrous or porous material, such as cotton, to prevent loss of nicotine. The term "matrix" is used in this context however for a completely different technical feature than in WO 88/01516 and US patent specification 5,820,876.

There is further known a TTS for nicotine from US patent specification 4,915,950, in which a depot layer (13) is arranged between an adhesive (14), acting as a control device, and an anchoring adhesive (12). The active substance depot layer may consist of a non-woven fabric (fleece) e.g. polyester, polyethylene, polypropylene, polyamides, rayon or cotton and may particularly consist of a 100% polyester non-woven. There is no disclosure or hint at all of the use of paper in or by this specification.

It has now been found that a TTS with a quality substantially improved compared with the known state of the art is obtained if instead of the known support materials, including particularly fabrics such as fleece, the carrier material is paper. Paper is distinguished fundamentally from fabrics including non-woven (fleece) by the fact that in it the cellulose fibers are joined to form a thin layer by strengthening. The cohesion of the fibers in the paper is effected - besides the mechanical adherence and the hooking-together of the fibers - by chemical bonds (hydrogen bonds) which are formed between the hydroxyl groups of the cellulose molecules in the course of the manufacture of the paper. This chemical bond is so strong that the tensile strength of paper can even exceed that of ordinary construction steel (RM Consult Papiermaschinen Info – <http://home.t-online.de/home/rm.consult/rm-info.htm> of November 17, 1998). In addition, paper has the advantage that it has a high absorption capacity for liquid phases which is characterized by DIN ISO 8787 by the height of suction. Thus the height of suction in the long direction determined for paper with a basis weight of 26 g/m<sup>2</sup> was 146 mm/10 min and in cross direction 143 mm/10 min compared with values of about 110 and 80 mm/10 min for the abovementioned fleece material Paratex III/40, where the values for the fleece varied to a very large extent in the serial tests. Paper ordinarily does not contain a binding agent, so that no incompatibilities can occur between active substance and binding agent.

Subject of the invention therefore is a transdermal therapeutic system containing as essential features

- a) a backing layer remote from the skin and impermeable for the active substance,
- 5 b) at least one active substance depot,
- c) a matrix contacting the active substance depot and controlling the delivery of the active substance, and
- d) a pressure-sensitive adhesive fixing device for the therapeutic system on the skin, the depot or the matrix or both containing support materials, wherein the support
- 10 material consists of paper.

Using paper as support material and inert adjuvant according to the invention has various advantages. When using fabrics, such as fleeces, there is always a certain range of deviation of the amount of active substance transferred to the single TTS, this being so in spite of a good dosing technique. For example, it has been observed that the amounts of nicotine transferred to the single TTS have a range of deviation of about 4% when using a fleece (70:30 viscose-cotton fiber blend, substance weight 40 g/m<sup>2</sup>). If according to the invention paper is used instead, the range of deviation is considerably smaller; dependent on the surface weight of the paper it is significantly

15 below 2%, e.g. with a paper having a basis weight of 23 g/m<sup>2</sup> below 1.9% and with paper having a basis weight of 26 g/m<sup>2</sup> even below 1.2%. The preferred papers have a basis weight of from 9 to 60, preferably from 15 to 40 and particularly from 20 to 35 g/m<sup>2</sup>.

25 The use of paper as support material in TTS according to the invention is, however, of importance not only for the uniformity of the TTS produced but also for the production technique. According to a known process a defined amount of the active substance is transferred to the support material by means of a tampon. This implies that in this process a certain amount of the support material is rubbed off by the

30 tampon and is entrained upon detaching of the tampon from the support material. This requires the tampon to be cleaned at certain intervals and thus the production process has to be interrupted. When using paper according to the invention the abrasion is significantly reduced, which can be explained by the fact that the fibers of paper are more firmly joined with each other than for example the fibers in a fleece or other fabric. It is known that fibrous fractions emanate from every fabric. It is made

35 possible by the use of paper according to the invention that the ability of the tampon to function is prolonged at least by 10 times, mostly even by 50 to 100 times, so that



its cleaning and accordingly an interruption of the production process are required much less frequently.

5 TTS according to the invention can be of various configurations. Suitable  
embodiments are shown in the attached Figures 1 and 2, although other  
embodiments are possible, as they are for example disclosed in international  
application WO 88/01516. According to Figures 1 and 2 the TTS consist of a backing  
layer (10), a reservoir matrix (12), one or more depots (14) and a fixing device (16)  
10 which are provided with a protective foil which is removed before administration so  
that the system is then fixed on the skin (18). The protective foil has also to be  
impermeable for the active substance, of course.

15 For the backing layer, the reservoir matrix, the fixing device and the protective foils,  
materials known to the skilled worker are used.

Subject of the invention is also a process for the improved production of transdermal  
therapeutic systems with a reduced range of deviation of the amounts of active  
substance applied, wherein the active substance is applied in conventional manner  
by means of a tampon to a support material which consists of paper. According to a  
20 preferred embodiment the deviation (relative standard deviation) of the amount of  
active substance applied, as achieved by the procedure of the invention, is less than  
2%, particularly below 1.2%.

25 A final subject of the invention consists in the use of paper as a support and  
distribution medium in transdermal therapeutic systems.

The systems according to the invention are in principle suitable for all active  
substances which can be administered transdermally. Particularly there may be  
named, in addition to those mentioned above, lidocaine, diphenylhydramine  
30 hydrochloride, salbutamol, 5-fluorouracil and as sexual hormone estradiol and also  
gestagens such as norethindrone acetate, levonorgestrel.

#### Example 1

35 First a pressure-sensitive adhesive preparation HS is prepared by homogenizing  
a) 933 g of a commercial product (®Durotak 387-2516 of the company National Starch  
and Chemical, Zutphen, the Netherlands— this is a 40% solution of a self-  
crosslinking acrylate polymer based on 2-ethylhexyl acrylate, vinyl acetate, acrylic

acid and titanium chelate ester in a solvent mixture of ethyl acetate, ethanol, heptane and methanol) with

- b) 8 g of a triglyceride of fractionated coconut fatty acids (C<sub>8</sub>-C<sub>10</sub>; ®Miglyol 812 of the company Hüls AG, Witten, Germany).

5

In addition 6210 g of ®Durotak 387-2516, 553 g of ethyl acetate and 311 g of ethanol are combined with 66 g of the aforementioned triglyceride and with 626 g of an acrylic resin prepared from dimethylaminoethyl methacrylate and neutral methacrylic acid esters (®Eudragit E 100 of the company Röhm-Pharma, Darmstadt, Germany) and

10

homogenized (adhesive composition MS).  
  
In addition 72 g of ®Eudragit E 100 are introduced into 101 g nicotine and dissolved therein. Thus the active substance preparation is obtained.

15

The pressure-sensitive adhesive composition HS is applied to a dehesively finished protective layer (A) such that after the evaporation of the solvents a pressure-sensitive adhesive layer is formed with a substance weight of 40 g/m<sup>2</sup>.

20

The adhesive composition MS is applied to a further dehesively finished protective layer (B) such that after evaporation of the solvents a film having a substance weight of 220 g/m<sup>2</sup> is produced. This film is laminated to the pressure-sensitive adhesive layer applied to the protective layer (A). Thus the lower sheet is obtained.

25

In a further coating step the adhesive composition MS is applied to a further dehesively finished protective layer (C) such that after evaporation of the solvents a film having a substance weight of 110 g/m<sup>2</sup> is produced upon which the backing layer impermeable for the active substance is laminated. Here the upper sheet is produced.

30

After removal of the dehesively finished protective layer (B) from the lower sheet there are positioned centrally disks made of a fleece fabric (70:30 viscose rayon-cotton fiber blend- substance weight 40 g/m<sup>2</sup>) or paper (26 or 24 g/m<sup>2</sup> respectively).

35

Subsequently the active substance preparation is dosed onto the disks of fleece material or paper, respectively.

After removal of the dehesively finished protective layer (C) the upper sheet is laminated to the lower sheet (finished with disks of fleece material or paper and

provided with active substance preparation), and transdermal therapeutic systems are punched therefrom. The results are evident from the following table:

<u>Number of TTS produced</u>	<u>Cleaning of the Tampon</u>	
	<u>Fleece material</u>	<u>Paper</u>
1,200	necessary	no
2,400	necessary again	no
3,600	necessary again	no
4,800	necessary again	no
more than 100,000	(continually after every 1,200 TTS)	no

- 5 As is evident from the table it is possible when using fleece material to produce only 1,200 transdermal therapeutic systems. Then cleaning of the device for transfer of the active substance (tampon) is required. Contrary thereto more than 100,000 transdermal therapeutic systems can be produced when using paper, without the need to shut down the machinery owing to cleaning becoming necessary.

10

#### Example 2

Transdermal therapeutic systems were produced according to Example 1 and the accuracy of the dosing was determined.

15

The amount of nicotine contained in the single transdermal therapeutic systems was determined and the results statistically evaluated. It was found that transdermal therapeutic systems which have been produced by using paper have a significantly smaller relative standard deviation (S-rel(%)) (see Figure 3).

## Claims

1. A transdermal therapeutic system containing as essential features
  - a) a backing layer remote from the skin and impermeable for the active substance,
  - 5 b) at least one active substance depot,
  - c) a matrix contacting the active substance depot and controlling the delivery of the active substance, and
  - d) a pressure-sensitive adhesive fixing device for the therapeutic system on
- 10 the depot or the matrix or both containing support materials, wherein the support material consists of paper.
- 15 2. The transdermal therapeutic system as claimed in claim 1, wherein the active substance is one or more sexual hormones, nitroglycerine, scopolamine, particularly however nicotine or a combination of sexual hormones.
- 20 3. A process for the improved production of a transdermal therapeutic system with reduced range of deviation of the amount of active substance applied, wherein the active substance is applied in conventional manner by means of a tampon to a support material which consists of paper.
- 25 4. The process as claimed in claim 3, wherein the deviation of the amount of active substance applied is less than 2%, particularly below 1.2%.
5. The embodiment as claimed in one or more of claims 1-4, wherein the paper has a basis weight of from 9 to 60, preferably from 15 to 40 and particularly from 20 to 35 g/m<sup>2</sup>.
- 30 6. The use of paper as a support and distribution medium in a transdermal therapeutic system.

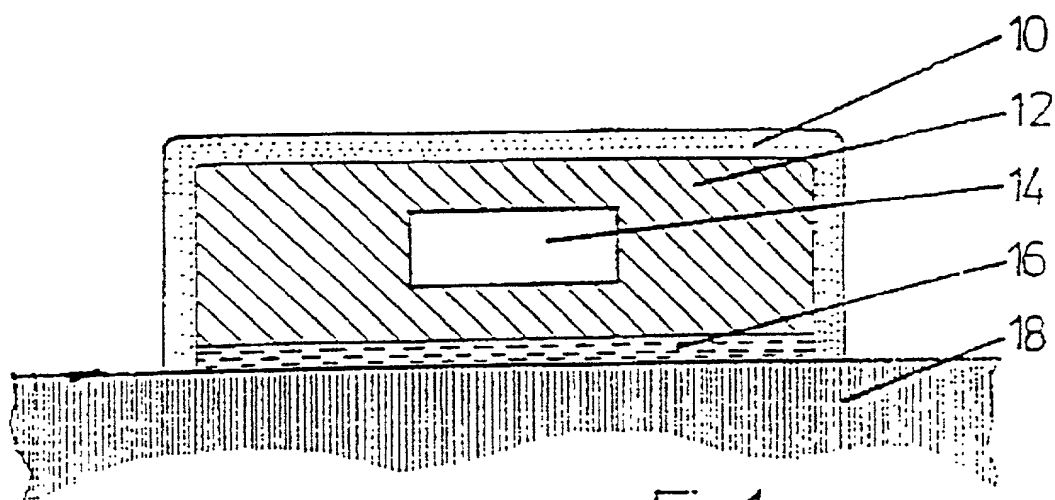


Fig.1

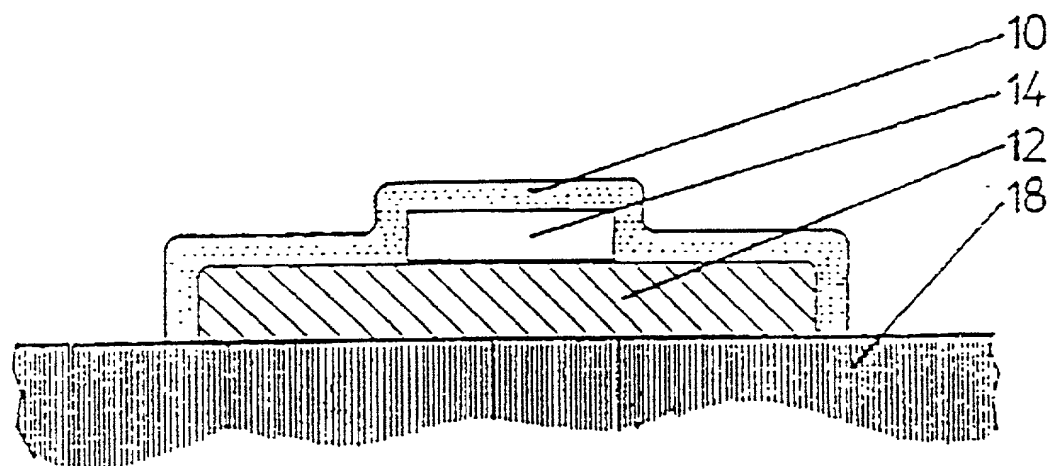
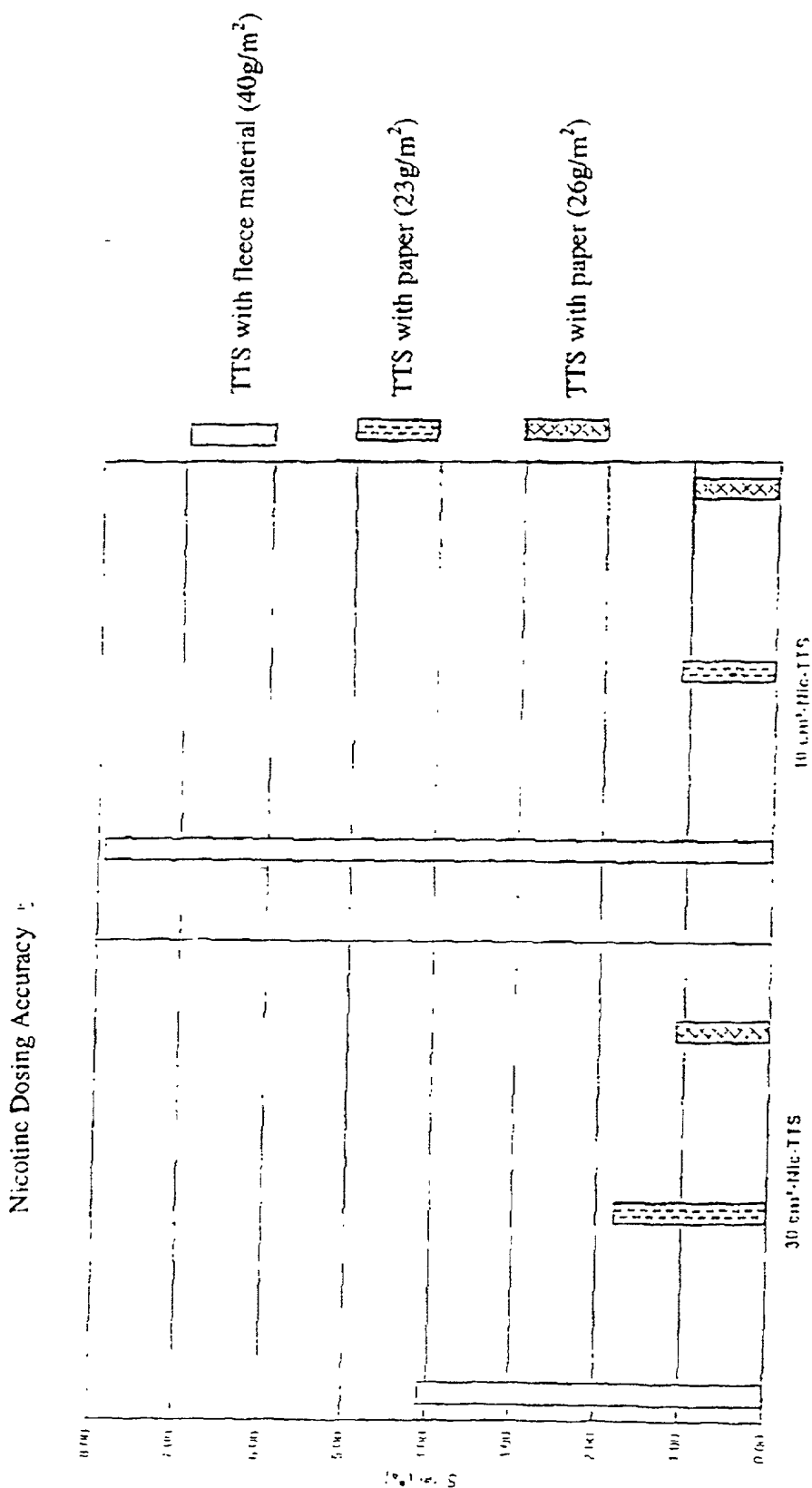


Fig.2

Figure 3



**COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY**

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**Transdermal Therapeutic System and Process for its Production**

the specification of which

- is attached hereto
- was filed on

and including all the amendments through the date hereof.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application (s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

**Prior Foreign Application (s) for which Priority is Claimed:**

- 1.) U.S.A., 60/124.957 of March 18, 1999
- 2.) Federal Republic of Germany, 19912477.9 of March 19, 1999

And I hereby appoint

William F. Lawrence, Registration No. 28,029, of the firm FROMMER LAWRENCE & HAUG, LLP whose post office address is 745 Fifth Avenue, New York, New York 10151, or their duly appointed associate, my attorneys, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to file continuation and divisional application thereof, to receive the Patent, and to transact all business in the Patent and Trademark Office and in the Courts in connection therewith, and specify that all communications about the application are to be directed to the following correspondence address:

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745 Fifth Avenue  
New York, New York 10151

Direct all telephone calls to:  
 (212) 588-0800, to the attention  
 of : William F. Lawrence

1999/109 US

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Date: 24. 7. 01

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Date: 19. 7. 01

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